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GUEST EDITORIAL

5-Year Cure Rate: Yet Another Myth

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''It is very depressing to live in an era when it is easier to split an atom than a myth.'' (A. Einstein)

The 5-year survival rate has long been cited as an index of the effectiveness of cancer treatment. It has been in wide use since the end of the nineteenth century, included in thousands of scientific publications. Basically, the 5-year survival rate is a statistical tool for characterizing the survival of a certain group of individuals. It is somewhat primitive [1,2], since it does not utilize all available information from a survival analysis. It tells us only how large a proportion has survived for a limited time-span—arbitrarily put to 5 years. It is not even a true rate, but simply a value at a fixed point of time [3]. In fact, it is easy to give examples of quite different survival patterns with identical 5-year survival rates (Fig. 1).

If the original intention with the ''5-year survival'' had been maintained—as a mere value in time—no harm would have been done. But over the years a change has occurred in the meaning—interpretation?—of the term ''5-year survival rate.'' It has gradually shifted to become the equivalent to ''5-year-cure rate.'' This is a gross misconception, because ''survival'' is not synonymous with ''cure.'' Only for fast-growing tumors (e.g., acute leukemias and testicular nonseminomatous germ cell tumors) is surviving for 5 years after the diagnosis likely to indicate a true cure. This is illustrated by curve B in Figure 1. Most human malignancies, however, are slow-growing [4,5], i.e., most cancers of the breast, colon, or prostate, and require many years or even decades to kill their host. For such cases, survival for 5 years is not indicative of cure. For example, of the women who survive their breast cancer diagnosis for 5 years, 1/3 will succumb to their disease, and for those women who survive for 10 years, as much as 1/4 will still die from their malignancy. Even as long as 30 years after the diagnosis, this patient population shows an excess mortality from cancer of the breast. Consequently, some clinicians have posed the question: Do we ever cure cancer of the breast? [6–21].

Apart from being arbitrary and providing only curtailed information, any limited observation period (such as 5 years) also has the disadvantage of allowing one additional pitfall: ''lead time bias'' [22–24]. If the time of diagnosis is shifted to an earlier date, the fixed observation period will automatically lead to fewer observed deaths at the end of that period. The impression is, therefore, given that ''early diagnosis leads to better prognosis.'' This conclusion is erroneous: Shifting the time of diagnosis of a patient to an earlier date means only that the patient (if untreated) will live longer as a cancer patient, although not as an individual.

The cliché ''earlier diagnosis leads to better prognosis'' and the misconception ''5-year cure'' have done more harm than good. The cliché lacks firm scientific support, and the words ''early'' and ''cure'' are often used without being defined. If ''early'' is supposed to mean ''before the tumor has metastasized,'' this is another illusion. Most human tumors have metastasized when diagnosable by present-day methods [25–30]. Further, the word ''cure'' should be used with caution. Many adult malignant tumors have a long natural course extending over two or three decades [4,5]. This means that there are many individuals who, after having had their primary tumors removed, live with asymptomatic, microscopic disease (like many other chronic diseases). These patients have not been cured, but they live seemingly healthy lives with ''no evidence of disease.''

In clinical oncology, a wholly satisfactory definition of the term ''cure'' is, therefore, regarded as difficult—if not almost impossible [19]. There are three current definitions of cure: (1) statistical, (2) clinical, and (3) personal. ''Statistical cure'' means that the study population dies at the same rate as the ''normal'' population (regardless of diagnosis). ''Clinical cure'' designates the

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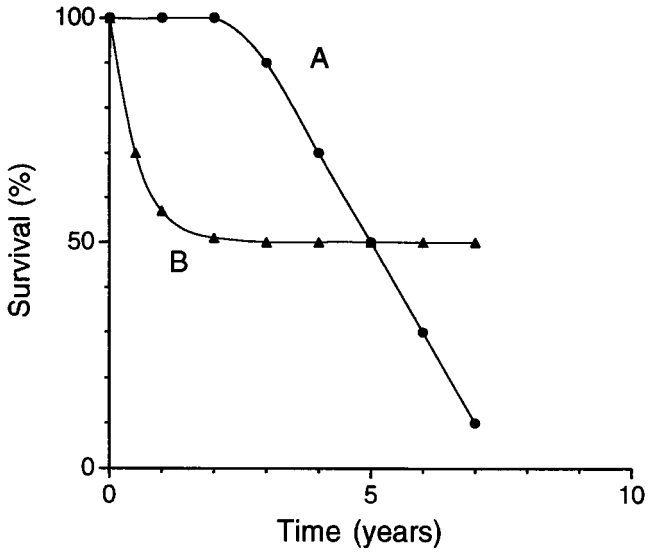

Fig. 1. Two series with identical 5-year survival rates (50%). Survival in series A is better for the first 4 years, but practically nil after 7 years. Survivors in series B can be regarded as cured after 3 years.

situation in which the study population dies of its malignancy at the same rate as the ''normal'' population (with the same diagnosis). ''Personal cure'' means that the study population dies *with* its disease, but not *from* it (i.e., death from cardiovascular disease, but with known active tumor). It is a paradox that whatever definition of ''cure'' is chosen, the patient must die—and be autopsied—before he or she can be declared healthy.

Thus, regardless of which of these definitions is intended, a 5-year survival period should not be equated with ''cure'' for most malignancies. In spite of this, the ''5-year cure rate'' has been hammered into the heads of the public, the medical profession, journalists, the legal profession, and many others, for so long that it has become an axiom. It is written in the minds of the people, in publications, and in textbooks.

The use—or rather misuse—of the term ''5-year survival'' has been criticized by statisticians since the 1940s [1–3,6,31]. In spite of this, it has not only survived (for more than 5 years!), but it has grown to become regarded as an endpoint. Endpoint of what?

It is not an endpoint in a clinical trial, not the endpoint of the course of a disease, not an endpoint of an observation or a follow-up period [32]. We tend to hold fast to the clichés of our teachers, enjoying the comfort of popular opinion, simultaneously avoiding the discomfort of thought.

If a false statement—i.e., surviving for 5 years means cure—is repeated sufficiently often, it will be accepted as a truth. It is noteworthy that clearsighted criticism of the medical clichés, terms, and misconceptions does not come from a profession *with* a medical education, but from one without such an education: the legal society [33,34].

The illusion created by the 5-year cure rate gives false promises based on false premises. Bitter frustration among patients (who experience recurrences and/or metastasis 10 or 15 years after the first 5-year period), confusion and denial in the medical profession, and lawsuits against doctors [35]. The delayed diagnosis of breast cancer is now the most frequent medical malpractice claim in the United States, and ''it is the second most expensive condition for insurers to indemnify'' [36].

If we are to make any progress in the war against cancer, we must first recognize the limitations set by nature.

''The single most characteristic human ability is that we can handle a complex language fluently. We can use words to denote not only objects and events in the outside world but also more abstract concepts. This ability leads to another striking human characteristic, one that is seldom mentioned: our limitless capacity for self-deception'' (F. Crick) [37].

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COMMENTARY

In criticizing the time-honored ''five-year survival rate,'' Friberg has pinpointed a common misrepresentation; one that predisposes to false claims of success and deceives both the provider as to the benefit of his labor and the patient who is given false expectations.

Cancers possess highly variable growth rates [1,2]. Slower-growing, indolent cancers are more likely to be discovered by periodic screening called length biased sampling. Patients with these cancers live longer because the cancers are found earlier in their natural history and grow more slowly. When relating this latter group to a fixed end-point, 5- or 10-year survivorship, conclusions as to benefit are subject to a lead time bias. Even the common statement, ''If you diagnose cancer early, you can cure it,'' is subject to bias. ''If'' does not establish that the objective is obtainable and it clearly does not apply to many cancers, i.e., pancreas, lung, etc. ''Early'' is undefined in this statement. Cancers that disseminate before they are discoverable have no early stage in the world of clinical reality.

There are more concise and insightful ways of measuring the benefits of treatment. Haybittle [3], for example, analyzed all the controlled clinical trials for breast cancer and concluded that none provide evidence of a statistical cure, and that all people die at a fairly predictable rate known as the ''force of mortality.'' A lethal disease like breast cancer increases the force of mortality. If therapeutic intervention is successful, the force of mortality *after* treatment parallels the *expected* force of mortality. This is referred to as a statistical cure. False conclusions of benefit are reached when reporting stage-specific, fixed end-point, 5- and 10-year survival rates. Sadly, population data establish that the age-adjusted probability of dying of breast cancer has not changed significantly in the U.S. since accurate record keeping began in 1930 [4].

Though there is much hue and cry for tort reform and alleged delay in the diagnosis of cancer is a leading cause of malpractice litigation, physicians still fail to acknowledge the fact that the underlying cause of these claims may often be the biases associated with the use and interpretation of stage-specific, fixed end-point, i.e., 5- and 10-year survival rates, ignoring the more meaningful force of mortality and the concept of a statistical cure.

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